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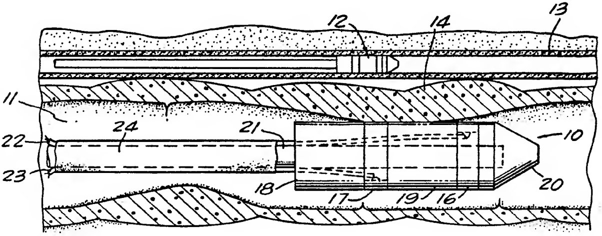
(54) Probe and method of use for detecting abnormal tissues.

(57) Two probes (10,12) for tissue impedance measurement each have first and second conductive rings (16,17) unitarily arranged with an insulative member (19) separating the rings. The conductive rings are coaxially arranged and have individual lead wires (22,23) connected thereto which extend from one end of the probe for connection to external processing and measuring equipment. One probe (12) is of a size enabling insertion within a blood vessel (13) while the other (10) is for location in an epithelial cavity (11). In use an alternating test signal is applied to the electrodes of each probe and measurements are taken between the two sets of measuring electrodes determining the impedance of the cavity wall tissue (14) lying between the two probes without passing current through the tissue.

FIG. 5



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PROBE AND METHOD OF USE FOR DETECTING ABNORMAL TISSUES

The present invention pertains generally to the detection of the presence of and tendency toward abnormal tissue growth and, more particularly, to a probe and method of use of the probe for the detection of abnormal tissue and an early indication that tested tissue will become abnormal.

BACKGROUND

The term "abnormal tissue" as used herein refers to all forms of tissues which have undergone malignant induction such that these tissues may eventually show loss of growth control which is frequently referred to as cancerous or tumorous growth. The detection of the presence of such abnormal tissues is often made difficult because they are located within the body so that until discomfort or other symptons are experienced by the individual, the existence of the abnormal tissues may not even be suspected. Additionally, procedures for early detection can be so expensive and complex as to make their use restricted. Therefore, it would be highly advantageous to be able to detect quickly and simply the presence of abnormal tissue or ideally the eventuality of abnormal tissue growth within a body cavity of the host, for example, and preferably the technique should be minimally invasive.

Many forms of cancers or tumors require extended periods of time to achieve a size detectable or injurious to the host, and in some cases this may take many years. Treatment at the present time is considerably more effective when the abnormal tissues are in their early phases and long before they have achieved growth sufficient to cause discomfort or produce symptons. It would, therefore, also be advantageous to be able to detect the presence of abnormal tissues in their early phases or to detect the tendency for tissues to become abnormal.

Several research efforts have been directed toward discovering the relationship between the electrical impedance of biological tissue and its condition or health. For example, U.S. Patent 3,949,736 discloses that the impedance of biological tissues can provide a useful indication as to whether tissues are healthy or diseased. Specifically, this patent suggests that changes in impedance of biological tissues can be used as a technique for diagnosis of certain carcinomas. According to this patented technique, a low level electric current is passed through the investigated tissue with measurement of the voltage drop across the tissue providing an indirect indication of the overall tissue impedance (i.e., resistance and capacitance). Also, according to this patent, increase in the impedance of the tissue is associated with an abnormal condition of the cells composing the tissue and indicative of a tumor, carcinoma, or other abnormal biological condition of the tissue.

SUMMARY OF THE DISCLOSURE

A probe for use in effecting measurements of tissue impedance consists of first and second conductive rings unitarily arranged with an insulative member separating the rings. The conductive rings, one a measuring and the other a working electrode, are generally coaxially arranged and have individual lead wires connected thereto which extend from one end of the probe for connection to external processing and measuring equipment.

A second probe, which may be constructed in the same manner as the first probe, has electrodes each consisting of annular conductors mounted within an elongated insulative tubular member substantially smaller than the probe, and, in particular, are of a size and shape enabling their receipt within a blood vessel, for example.

In use, the first probe containing one set of electrodes is inserted within an epithelial cavity (e.g., the colon) and located at a test position through the use of an endoscope. Then the second probe is passed along a suitable blood vessel which may be located adjacent to the wall of the tissue defining the epithelial cavity within which the first probe is located. Optionally, the second probe may be located in the skin (either intradermal or subcutaneous), on the skin outer surface, or within a relatively remote blood vessel. An alternating test signal is then applied to the working electrodes of each probe and measurements are taken between the two sets of measuring electrodes determining the impedance of the cavity wall tissue lying between the two probes.

The external measuring and processing system consists of a microcomputer which automatically

controls a programmable impedance (resistance and capacitance) for balancing with the measured impedances between the probes, and displaying onto a CRT or other suitable output display device the information obtained. The AC input to the working electrodes is selectable to any desired frequency value over an extensive frequency range (10Hz-7Hz).

DESCRIPTION OF THE DRAWING

Figure 1 is a schematic view of the measuring and working electrodes shown interconnected with control and processing equipment.

Figure 2 is a side elevational, sectional view of an impedance probe of the present invention having two measuring electrodes and interconnecting lead wires.

Figures 3 and 4 are end elevational, sectional views taken along the lines 3-3 and 4-4 of Figure 2, respectively.

Figure 5 is a side elevational, partially fragmentary view showing the probe and working electrodes in place within the body of the individual.

Figures 6A and 6B show, respectively, electrical circuit schematics of the two stages for measuring tissue impedance.

Figure 7 is a graph of average tissue impedance measurements taken with the described probe and control and processing equipment.

DESCRIPTION OF A PREFERRED EMBODIMENT

Turning now to the drawings and particularly Figure 5, there is shown a probe 10 to be more particularly described which can be readily located within an epithelial cavity 11 of a test subject. The probe 10 in use electrically interacts with a second probe 12 selectively positioned in a blood vessel 13 to measure the impedance of the tissues 14 lying between the two probes.

As has been alluded to generally, and as will be more particularly described later therein, it is a basic premise of the present invention that the magnitude of electrical impedance of the tissues provides a direct indication as to the health or diseased condition of these tissues. It is believed, therefore, that the described techniques will be highly useful in the diagnosis of most epithelial carcinomas such as lung, colon rectum, cervix, pancreas, bladder, oro-pharynx, naso-pharynx, vagina, urethra, renal calyx, trachea, gall bladder, bile ducts, and small bowel, for example.

As can be seen best in Figure 2, the probe 10 includes first and second annular metallic electrodes 16 and 17 unitarily assembled with first and second insulative cylinders 18 and 19 and an insulative nose 20. The nose is generally conical and is affixed onto a circular side of the first electrode 16, the opposite side of this electrode being secured to the end wall surface of insulative cylinder 19. Similarly, the second electrode 17 has one side wall affixed to the end wall of cylinder 19 and the other side wall secured to the first insulative cylinder end wall surface.

The electrodes 16 and 17 along with the insulative cylinders 18, 19 and the nose 20 are assembled into a unitary cylindrical affair, the outer surface of which is smooth. A rod-like member 21 extends through the axially arranged bores of the insulative cylinders and electrodes and has its inner end embedded within the nose 20.

A first lead wire 22 extends along the member 21 and has one end conductively secured to an inner part of the electrode 16. A second lead wire 23 extends along the opposite side of member 21 through the bore of cylinder 18 and has its inner end conductively secured to an inner surface of electrode 17. Preferably, the cable wires 22 and 23 are enclosed with the member 21 by a smooth insulative covering 24 to protect surrounding tissues when the probe is being inserted into and removed from the body of a test subject.

Although other materials may be found suitable for constructing a probe 10, best results to date have been obtained by making annular electrodes 16 and 17 from silver which is coated with silver chloride ($AgCl_2$). This coating increases the electrode surface area approximately 10,000 times which reduces a problem sometimes referred to by the term "electrolytic polarization impedance" to be discussed in detail later herein.

The cylinders 18, 19 and the nose 20 are preferably constructed of a molded or machined synthetic plastic which is non-toxic, a good electrical insulator and can be brought to a highly smooth condition. Suitable materials for this purpose are nylon or the plastic sold under the commercial designation Delryn.

The second probe 12 is preferably constructed in the same manner as probe 10 with a pair of highly conductive cylinders separated by insulative members. The probes 10 and 12 are of a size commensurate with their ultimate use location. Thus, if contemplated for intravenous disposal, they are relatively small, whereas if considered for emplacement within, say, the colon, they can be correspondingly larger.

Biological tissue such as tissue 14 consists generally of semisolids and liquids which from the standpoint of their electrical characteristics act as electrolytes. The interface between the electrolyte and an electrode produces a so-called electrode-polarization impedance on the passage of an electric current therethrough, which can be of such magnitude as to impose a serious error in any tissue impedance measurement, and, therefore, compensation or elimination must be provided. The electrode silver chloride coating by increasing the electrode surface area (e.g., approximately 10,000 times) substantially reduces the electrolytic impedance. However, even with this coating the electrolytic impedance problem cannot be satisfactorily solved in 2-electrode measurement of tissue impedance (i.e., measuring the impedance by passing current through tissues lying between two electrodes). One approach to compensating for electrolytic impedance is to adopt a 4-electrode system, and this general scheme is adopted here. For a detailed discussion of theoretical aspects of this general approach reference is made to the article entitled, "An Operational Amplifier 4-Electrode Impedance Bridge for Electrolyte Measurements" by C. D. Ferris and Donald R. Rose in Medical Biological Engineering, Volume 10, pages 647-654, 1972.

For the ensuing discussion of the electrical control and tissue impedance measurement equipment used with the probe 10 and work electrodes 16, 17, reference is now made to Figure 1. A programmable oscillator 25 is selectively variable to provide test voltage in a range from 10Hz-7Hz. The alternating current output of oscillator 25 is applied to a bridge transformer 26 which is interconnected through a switch network 27 and bridge amplifier 28 to apply the selected oscillating voltage signal across certain of the probe electrodes as will be discussed in detail later. In addition, the switch network and bridge amplifier interconnect the electrodes of the two probes 10 and 12 with first and second programmable impedances 29 and 30. Biological tissues do not exhibit electrical inductance characteristics, and, therefore, the programmable impedances are further identified by the schematic representations "R1 C1", "R2 C2".

Figures 6A and 6B depict, respectively, first and second circuital arrangements used to accomplish what is a two stage tissue impedance measurement. In the first stage circuit, one side of the oscillating voltage signal from the bridge transformer 26 is applied to electrode 17 of probe 10 (which may be termed a "working" electrode) while the electrode 16 (a "measuring" electrode) is fed as one input to a differential amplifier 31. The other terminal of transformer 26 is connected to a common point of the parallel programmable resistance-capacitance arrangement identified as "R1 C1" the other common point of which connects with electrical ground and a working electrode of probe 12. The other, a measuring electrode of probe 12, serves as a second input to differential amplifier 31. The transformer other terminal is fed to a further amplifier 32. The amplification factors of amplifiers 31 and 32 are the same. The signal outputs of amplifiers 31 and 32 feed into bridge amplifer 28, also a differential amplifier.

The first stage measurement provides a first order approximation of the tissue impedance which is the programmed value of "R1/C1" when the bridge circuit is balanced. It is of particular importance to note that in making this measurement virtually no current passes through the tissue 14 and, therefore, the possibility of an error from electrolytic polarization impedances is obviated.

On conclusion of the first stage impedance measurement, the microcomputer 33 (Figure 1) effects via switch network 27 a substitution of a second set of programmable impedances, R2 C2, for the probes 10 and 12. More particularly, one common point of R2 C2 is connected to the grounded common of R1 C1. The remaining common point of R2 C2 is fed into amplifier 31, the other input being grounded. Adjustment of R2/C2 is then made under control of the microcomputer following which the value of R2 C2 represents a precise measurement of the tissue impedance after the bridge circuit is balanced.

The second stage of balancing "R2/C2" against "R1 C1" acts to neutralize distributed impedances associated with cabling and internal equipment and circuit sources.

Still further as to overall system operation, unbalanced bridge amplifier signals are peak detected at 38, and coverted to digital form in the analog-to-digital converter 39 for insertion into the microcomputer. The computer, in turn, automatically adjusts the values of "R1 C1" until the bridge is balanced as indicated by the digital value returned by the A/D converter. Then, in the second stage the adjusted value of R1 C1 is maintained and R2 C2 is adjusted to bridge balance with the final value of R2 C2 being the tissue impedance.

As shown, operation is preferably under the control of a microcomputer 33 which may have a conventional set of peripherals, such as disc drive 34, cathode ray tube display 35 ("CRT"), key board 36, and printer 37. The values of R2 C2 and R1 C1 are automatically changed to achieve the highly accurate two-stage measurement of tissue impedance. A single output frequency of oscillator 25 can be selected by

inserting a proper command via keyboard 36. for example, or the computer program can specify another frequency or consecutive set of frequencies desired for impedance measurement. Also, a graphical representation of tissue impedance values measured can be displayed at the CRT 35 and printed out in desired manner at 37.

Figure 7 is a graph showing a number of impedance traces taken of various test subjects and over an extended frequency range of test voltage. The straight line traces are measurements made of test animal tissues with inbred resistance to abnormal tissue growth not otherwise known to be diseased. and which animals had been given fourteen (14) weekly injections of physiological saline, and, therefore, are concluded to be "healthy" tissues. The dotted line traces, on the other hand show tissue impedance values obtained from test animals which had received 14 weekly injections of DMH (dimethylhydrazine) a known carcinogen. the majority of which animals develop tumors after twenty-six (26) weeks of injections. As the graph clearly shows, the capacitance of healthy tissues is substantially greater than that of tissues which will eventually develop tumors. Measurements of electrical resistance alone at the same intervals have shown no significant change.

The use of DMH in laboratory animals is generally accepted as a model of large bowel cancer similar to spontaneously occuring cancer in man. See in this connection the comments of N. Thurnherr. E. E. Deschner, E H. Stonehill, M. Lipkin, in Cancer Research, Volume 33. page 940 (1973).

The graph of Figure 7 depicts the average values of ten (10) different test subject measurements (straight line) as compared with traces taken for the same number of test subjects injected with DMH. The results clearly show that healthy tissue has a substantially greater and definable capacitance than that of the tissues which will become abnormal.

A microcmputer 33 used in a practical constructed of the invention is a single-board microcomputer manufactured by Apple Computer and accomplished the described functions under control of the following program:

I/O ASSEMBLY SUBROUTINES

```
4100:        22 ;   $4000  16384  MODE
4100:        23 ;
4100:        24 ;   $4001  16385  FREQ
4100:        25 ;
4100:        26 ;   $4002  16386  GAIN RES      10^0
4100:        27 ;   $4003  16387                10^1
4100:        28 ;   $4004  16388                10^2
4100:        29 ;   $4005  16389                10^3
4100:        30 ;
4100:        31 ;   $4006  16390  BRIDGE GAIN
4100:        32 ;
4100:        33 ;   $4007  16391     R1         10^0
4100:        34 ;   $4008  16392                10^1
4100:        35 ;   $4009  16393                10^2
4100:        36 ;   $400A  16394                10^3
4100:        37 ;
4100:        38 ;   $400B  16395     C1         10^-4
4100:        39 ;   $400C  16396                10^-3
4100:        40 ;   $400D  16397                10^-2
4100:        41 ;   $400E  16398                10^-1
4100:        42 ;
4100:        43 ;   $400F  16399     R2         10^0
4100:        44 ;   $4010  16400                10^1
4100:        45 ;   $4011  16401                10^2
4100:        46 ;   $4012  16402                10^3
4100:        47 ;
4100:        48 ;   $4013  16403     C2         10^-4
4100:        49 ;   $4014  16404                10^-3
4100:        50 ;   $4015  16405                10^-2
4100:        51 ;   $4016  16406                10^-1
4100:        52 ;
4100:        53 ;   $4017  16407  BRIDGE VALUE
4100:        54 ;
4100:        55 ;   $4018  16408  TEMP MEMORY USAGE
4100:        56 ;
4100:        57 ;   - - - - - - - - - - - - - - - - - - - - - -
```

```
4100:                  58 ;
4100:                  59 ;          PIA INITIALIZATION ROUTINE
4100:                  60 ;
4100:EA                61 INIT      NOP
4101:A9 30             62           LDA   #$30
4103:8D 01 C3          63           STA   $C301          LOAD CRA-A
4106:8D 03 C3          64           STA   $C303          LOAD CRB-A
4109:8D 05 C3          65           STA   $C305          LOAD CRA-B
410C:8D 07 C3          66           STA   $C307          LOAD CRB-B
410F:A9 FF             67           LDA   #$FF
4111:8D 00 C3          68           STA   $C300          SET DDRA-A AS OUTPUT
4114:8D 04 C3          69           STA   $C304          SET DDRA-B AS OUTPUT
4117:8D 06 C3          70           STA   $C306          SET DDRB-B AS OUTPUT
411A:A9 00             71           LDA   #$00
411C:8D 02 C3          72           STA   $C302          SET DDRB-A AS INPUT
411F:A9 34             73           LDA   #$34
4121:8D 01 C3          74           STA   $C301          SET CA2-A (   RC CLK    ) LOW
4124:8D 03 C3          75           STA   $C303          SET CB2-A (             ) LOW
4127:8D 05 C3          76           STA   $C305          SET CA2-B (OSC/MODE CLK) LOW
412A:8D 07 C3          77           STA   $C307          SET CB2-B (   RG CLK    ) LOW
412D:                  78 ;
412D:                  79 ;           INITIAL VALUE SETTINGS
412D:                  80 ;
412D:A2 FF             81           LDX   #$FF
412F:A9 00             82 AGN1      LDA   #$00
4131:9D 00 40          83           STA   $4000,X        CLEAR VARIABLES
4134:CA                84           DEX
4135:F0 03    413A     85           BEQ   NXT1
4137:4C 2F 41          86           JMP   AGN1
413A:A9 00             87 NXT1      LDA   #$00
413C:8D 00 40          88           STA   $4000          SET CAL MODE
413F:A9 00             89           LDA   #$00
4141:8D 01 40          90           STA   $4001          OSCILLATOR OFF
4144:A9 04             91           LDA   #$04
4146:8D 05 40          92           STA   $4005          SET GAIN RES TO 4K
4149:A9 00             93           LDA   #$00
414B:8D 06 40          94           STA   $4006          SET BRIDGE GAIN TO 1
414E:A9 01             95           LDA   #$01
4150:8D 0A 40          96           STA   $400A          SET R1 TO 1K
```

```
4153:A9 01          97            LDA   #$01
4155:8D 0E 40       98            STA   $400E       SET C1 TO .1000 uf
4158:A9 01          99            LDA   #$01
415A:8D 12 40      100            STA   $4012       SET R2 TO 1K
415D:A9 01         101            LDA   #$01
415F:8D 16 40      102            STA   $4016       SET C2 TO .1000 uf
4162:4C 66 41      103            JMP   LOAD
4165:60            104            RTS
4166:              105 ;
4166:              106 ;                  I/O ROUTINE
4166:              107 ;
4166:EA            108 LOAD       NOP
4167:AD 01 40      109            LDA   $4001       FREQUENCY CODE
416A:0A            110            ASL   A
416B:0A            111            ASL   A
416C:18            112            CLC
416D:6D 01 40      113            ADC   $4001       MODE CODE
4170:8D 04 C3      114            STA   $C304
4173:A9 3C         115            LDA   #$3C
4175:8D 05 C3      116            STA   $C305       SET CA2-B (OSC/MODE CLK) HIGH
4178:A9 34         117            LDA   #$34
417A:8D 05 C3      118            STA   $C305       SET CA2-B (OSC/MODE CLK) LOW
417D:A2 03         119            LDX   #$03
417F:8A            120 AGN2       TXA
4180:0A            121            ASL   A
4181:0A            122            ASL   A
4182:0A            123            ASL   A
4183:0A            124            ASL   A
4184:0A            125            ASL   A
4185:0A            126            ASL   A
4186:8D 04 C3      127            STA   $C304       GAIN RES ENABLE (RGE X)
4189:AD 06 40      128            LDA   $4006
418C:0A            129            ASL   A
418D:0A            130            ASL   A
418E:0A            131            ASL   A
418F:0A            132            ASL   A
4190:18            133            CLC
4191:7D 02 40      134            ADC   $4002,X
4194:8D 06 C3      135            STA   $C306       GAIN RES DATA (RGD X) & BRIDGE GAIN
4197:A9 3C         136            LDA   #$3C
4199:8D 07 C3      137            STA   $C307       SET CB2-B (RG CLK) HIGH
419C:A9 34         138            LDA   #$34
419E:8D 07 C3      139            STA   $C307       SET CB2-B (RG CLK) LOW
```

```
41A1:8A                 140            TXA
41A2:F0 04    41A8      141            BEQ    NXT2
41A4:CA                 142            DEX
41A5:4C 7F 41           143            JMP    AGN2
41A8:EA                 144 NXT2       NOP
41A9:A2 0F              145 LDRC       LDX    #$0F
41AB:8E 18 40           146 AGN3       STX    $4018
41AE:BD 07 40           147            LDA    $4007,X
41B1:0A                 148            ASL    A
41B2:0A                 149            ASL    A
41B3:0A                 150            ASL    A
41B4:0A                 151            ASL    A
41B5:18                 152            CLC
41B6:6D 18 40           153            ADC    $4018
41B9:8D 00 C3           154            STA    $C300        RC ENABLE (RCE X) & RC DATA (RCD X)
41BC:A9 3C              155            LDA    #$3C
41BE:8D 01 C3           156            STA    $C301        CA2-A (RC CLK) HIGH
41C1:A9 34              157            LDA    #$34
41C3:8D 01 C3           158            STA    $C301        CA2-A (RC CLK) LOW
41C6:8A                 159            TXA
41C7:F0 04    41CD      160            BEQ    NXT3
41C9:CA                 161            DEX
41CA:4C AB 41           162            JMP    AGN3
41CD:                   163 ;
41CD:                   164 ;                 READ BRIDGE VALUE
41CD:                   165 ;
41CD:EA                 166 NXT3       NOP
41CE:AD 02 C3           167 READ       LDA    $C302
41D1:8D 17 40           168            STA    $4017        BRIDGE VALUE
41D4:60                 169 END        RTS
```

MANUAL OPERATION SOFTWARE

```
200  REM
201  REM                VARIABLE LIST
202  REM
204  DIM FRQ(12): DIM FRQ$(12): REM              FREQUENCY VALUES
205 FRQ(0)  = 0:FRQ$(0)  = "OFF"
206 FRQ(1)  = 5:FRQ$(1)  = "20"
207 FRQ(2)  = 6:FRQ$(2)  = "50"
208 FRQ(3)  = 7:FRQ$(3)  = "70"
209 FRQ(4)  = 8:FRQ$(4)  = "100"
210 FRQ(5)  = 9:FRQ$(5)  = "200"
211 FRQ(6)  = 10:FRQ$(6)  = "500"
212 FRQ(7)  = 11:FRQ$(7)  = "700"
213 FRQ(8)  = 12:FRQ$(8)  = "1K"
214 FRQ(9)  = 13:FRQ$(9)  = "2K"
215 FRQ(10)  = 14:FRQ$(10)  = "5K"
216 FRQ(11)  = 15:FRQ$(11)  = "7K"
220  DIM MD(3): DIM MD$(3): REM                    MODE VALUES
221 MD(1)  = 0:MD$(1)  = "CAL"
222 MD(2)  = 1:MD$(2)  = "M1"
223 MD(3)  = 2:MD$(3)  = "M2"
```

```
230  DIM R1$(12): DIM C1$(12): REM                R1&C1 DISPLAY VALUES
231  DIM R2$(12): DIM C2$(12): REM                R2&C2 DISPLAY VALUES
232  FOR N = 1 TO 12
233 R1$(N) = " - ":C1$(N) = " - "
234 R2$(N) = " - ":C2$(N) = " - "
235  NEXT N
240  DIM BAL(12): DIM BAL$(12)
241  FOR N = 1 TO 12
242 BAL(N) =  PEEK (16389) * 1000 +  PEEK (16388) * 100 +  PEEK (16387) *
     10 +  PEEK (16386)
243 BAL$(N) =  STR$ (BAL(N))
244  NEXT N
250  DIM SYS$(10): REM                             SYSTEM MODES
251 SYS$(1) = "MAN"
252 SYS$(2) = "AUTO"
253 SYS$(3) = "BIT"
254 SYS$(4) = "STBY"
255 SYS$(5) = "AGC"
256 SYS$(6) = "BAL"
257 SYS$(7) = "R1"
258 SYS$(8) = "C1"
259 SYS$(9) = "R2"
260 SYS$(10) = "C2"
1000  REM
1001  REM           MENU CHOICES
1002  REM
1004  GOSUB 10000
1006 SYS = 4: GOSUB 11000
1008  VTAB 22: PRINT BELL$;"MANUAL OPERATION ? ";: GET ANS$: PRINT
1010  VTAB 22: PRINT  SPC( 38);""
1012  IF ANS$ = "Y" THEN  GOTO 2000
1014  VTAB 22: PRINT BELL$;"AUTO OPERATION ? ";: GET ANS$: PRINT
1016  VTAB 22: PRINT  SPC( 30);""
1018  IF ANS$ = "Y" THEN  GOTO 4000
1020  GOTO 1008
2000  REM
2001  REM            MANUAL MODE
2002  REM
2004 SYS = 1: GOSUB 11000
2006  VTAB 22: PRINT BELL$;"SET MODE ? ";: GET ANS$: PRINT
2008  VTAB 22: PRINT  SPC( 38);""
2010  IF ANS$ <  > "Y" THEN  GOTO 2026
2012  VTAB 22: PRINT BELL$;"1-CAL 2-M1 3-M2  ? ";: GET ANS$: PRINT
2014  VTAB 22: PRINT  SPC( 38);""
2016  IF ANS$ = "1" THEN MD = 0: GOTO 2024
2018  IF ANS$ = "2" THEN MD = 1: GOTO 2024
2020  IF ANS$ = "3" THEN MD = 2: GOTO 2024
2022  GOTO 2012
2024  GOSUB 12000: GOTO 2006
2026  VTAB 22: PRINT BELL$;"SET FREQUENCY ? ";: GET ANS$: PRINT
2028  VTAB 22: PRINT  SPC( 38);""
2030  IF ANS$ <  > "Y" THEN  GOTO 2056
2032  VTAB 22: PRINT BELL$;: INPUT "ENTER FREQ. (HZ) OR '0' FOR OFF : ";A
     NS$
```

```
2034  VTAB 22: PRINT  SPC( 38);""
2036  IF ANS$ = "0" THEN FRQ = 0: GOTO 2054
2038  FOR N = 1 TO 7
2040  IF ANS$ = FRQ$(N) THEN FRQ = N: GOTO 2054
2042  NEXT N
2044  IF ANS$ = "1000" THEN FRQ = 8: GOTO 2054
2046  IF ANS$ = "2000" THEN FRQ = 9: GOTO 2054
2048  IF ANS$ = "5000" THEN FRQ = 10: GOTO 2054
2050  IF ANS$ = "7000" THEN FRQ = 11: GOTO 2054
2052  GOTO 2032
2054  GOSUB 12000: GOTO 2026
2056  VTAB 22: PRINT BELL$;"SET BRIDGE GAIN ? ";: GET ANS$: PRINT
2058  VTAB 22: PRINT  SPC( 38);""
2060  IF ANS$ <  > "Y" THEN  GOTO 2076
2062  VTAB 22: PRINT BELL$;: INPUT "ENTER GAIN VALUE : ";ANS$
2064  VTAB 22: PRINT  SPC( 38);""
2066  FOR N = 0 TO 7
2068  IF  STR$ (2 ^ N) = ANS$ THEN GN = N: GOTO 2074
2070  NEXT N
2072  GOTO 2062
2074  GOSUB 12000: GOSUB 13026: GOTO 2056
2076  GOSUB 13000
2078  VTAB 22: PRINT BELL$;: INPUT "ENTER BALANCE VALUE (OR '0') : ";ANS$

2080  VTAB 22: PRINT  SPC( 38);""
2082  IF  VAL (ANS$) = 0 THEN  GOTO 2102
2084  IF 0 <  VAL (ANS$) < 10000 THEN  GOTO 2088
2086  GOTO 2102
2088  FOR N = 16386 TO 16389: POKE N,0: NEXT N
2090 A = 16385 +  LEN (ANS$)
2092  FOR N = 1 TO  LEN (ANS$): POKE A, VAL ( MID$ (ANS$,N,1))
2094 A = A - 1
2096  NEXT N
2098  GOSUB 13000
2100  GOTO 2078
2102  VTAB 22: PRINT BELL$;: INPUT "ENTER R1 VALUE (OR '0') ";ANS$
2104  VTAB 22: PRINT  SPC( 38);""
2106  IF  VAL (ANS$) = 0 THEN  GOTO 2126
2108  IF 0 <  VAL (ANS$) < 10000 THEN  GOTO 2112
2110  GOTO 2102
2112  FOR N = 16391 TO 16394: POKE N,0: NEXT N
2114 A = 16390 +  LEN (ANS$)
2116  FOR N = 1 TO  LEN (ANS$): POKE A, VAL ( MID$ (ANS$,N,1))
2118 A = A - 1
2120  NEXT N
2122  GOSUB 13000
2124  GOTO 2102
2126  VTAB 22: PRINT BELL$;: INPUT "ENTER C1 VALUE (OR '0') ";ANS$
2128  VTAB 22: PRINT  SPC( 38);""
2130  IF  VAL (ANS$) = 0 THEN  GOTO 2150
2132  IF 0 <  VAL (ANS$) < 10000 THEN  GOTO 2136
2134  GOTO 2126
2136  FOR N = 16395 TO 16398: POKE N,0: NEXT N
2138 A = 16394 +  LEN (ANS$)
2140  FOR N = 1 TO  LEN (ANS$): POKE A, VAL ( MID$ (ANS$,N,1))
2142 A = A - 1
2144  NEXT N
```

```
2146  GOSUB 13000
2148  GOTO 2126
2150  VTAB 22: PRINT BELL$;: INPUT "ENTER R2 VALUE (OR '0') ";ANS$
2152  VTAB 22: PRINT  SPC( 38);""
2154  IF  VAL (ANS$) = 0 THEN  GOTO 2174
2156  IF 0 <  VAL (ANS$) < 10000 THEN  GOTO 2160
2158  GOTO 2150
2160  FOR N = 16399 TO 16402: POKE N,0: NEXT N
2162 A = 16398 +  LEN (ANS$)
2164  FOR N = 1 TO  LEN (ANS$): POKE A, VAL ( MID$ (ANS$,N,1))
2166 A = A - 1
2168  NEXT N
2170  GOSUB 13000
2172  GOTO 2150
2174  VTAB 22: PRINT BELL$;: INPUT "ENTER C2 VALUE (OR '0') ";ANS$
2176  VTAB 22: PRINT  SPC( 38);""
2178  IF  VAL (ANS$) = 0 THEN  GOTO 2198
2180  IF 0 <  VAL (ANS$) < 10000 THEN  GOTO 2184
2182  GOTO 2174
2184  FOR N = 16403 TO 16406: POKE N,0: NEXT N
2186 A = 16402 +  LEN (ANS$)
2188  FOR N = 1 TO  LEN (ANS$): POKE A, VAL ( MID$ (ANS$,N,1))
2190 A = A - 1
2192  NEXT N
2194  GOSUB 13000
2196  GOTO 2174
2198  GOTO 1006
9999  END
10000  REM
10001  REM              DISPLAY FORMAT
10002  REM
10004  HOME :T$ = "A M E R I C A N   M E D I S C A N"
10006  HTAB 20 -  INT ( LEN (T$) / 2): PRINT T$
10008  PRINT "--------------------------------------"
10010  VTAB 3: PRINT  SPC( 38);""
10012  VTAB 3: INVERSE
10014  PRINT "SYS";
10016  HTAB 10: PRINT "MODE";
10018  HTAB 19: PRINT "FREQ";
10020  HTAB 30: PRINT "GAIN"
10022  NORMAL
10024  PRINT "--------------------------------------": PRINT
10026  HTAB 1: PRINT "FREQ";
10028  HTAB 7: PRINT "BAL";
10030  HTAB 14: PRINT "R1";
10032  HTAB 22: PRINT "C1";
10034  HTAB 29: PRINT "R2";
10036  HTAB 37: PRINT "C2"
10038  VTAB 8
10040  FOR N = 1 TO 11
10042  HTAB 4 -  LEN (FRQ$(N)): PRINT FRQ$(N)
10044  NEXT N
10046  VTAB 20: PRINT "--------------------------------------"
10048  VTAB 21: HTAB 25: PRINT "VALUE : "
10050  RETURN
```

```
11000  REM
11001  REM           DISPLAY SYSTEM DATA
11002  REM
11004  VTAB 3: HTAB 5: PRINT SYS$(SYS); SPC( 5 -  LEN (SYS$(SYS)));""
11006 MD =  PEEK (16384)
11008  VTAB 3: HTAB 15: PRINT MD$(MD + 1); SPC( 1);""
11010 FRQ =  PEEK (16385)
11012  FOR N = 0 TO 11
11014  IF FRQ(N) = FRQ THEN FRQ = N: GOTO 11020
11016  NEXT N
11018  GOTO 11022
11020  VTAB 3: HTAB 24: PRINT FRQ$(FRQ); SPC( 6 -  LEN (FRQ$(FRQ)));""
11024 GN$ =  STR$ (2 ^ ( PEEK (16390)))
11026  VTAB 3: HTAB 35: PRINT GN$; SPC( 4 -  LEN (GN$));""
11028  RETURN
12000  REM
12001  REM          SET MODE,FREQ,GAIN
12002  REM
12004  POKE 16384,MD
12006  POKE 16385,FRQ(FRQ)
12008  POKE 16390,GN
12010  CALL 16742
12012  GOSUB 11000
12014  RETURN
13000  REM
13001  REM           BAL,R1,C1,R2,C2,VALUE / FREQ
13002  REM
13003  IF FRQ = 0 THEN  RETURN
13004 BAL$(FRQ) =  STR$ ( PEEK (16389) * 1000 +  PEEK (16388) * 100 +  PEEK
     (16387) * 10 +  PEEK (16386))
13006 R1$(FRQ) =  STR$ ( PEEK (16394) * 1000 +  PEEK (16393) * 100 +  PEEK
     (16392) * 10 +  PEEK (16391))
13008 C1$(FRQ) = "." +  STR$ ( PEEK (16398)) +  STR$ ( PEEK (16397)) +  STR$
     ( PEEK (16396)) +  STR$ ( PEEK (16395))
13010 R2$(FRQ) =  STR$ ( PEEK (16402) * 1000 +  PEEK (16401) * 100 +  PEEK
     (16400) * 10 +  PEEK (16399))
13012 C2$(FRQ) = "." +  STR$ ( PEEK (16406)) +  STR$ ( PEEK (16405)) +  STR$
     ( PEEK (16404)) +  STR$ ( PEEK (16403))
13014  VTAB 7 + FRQ: HTAB 5: PRINT  SPC( 35);"": VTAB 7 + FRQ
13016  HTAB 10 -  LEN (BAL$(FRQ)): PRINT BAL$(FRQ);
13018  HTAB 17 -  LEN (R1$(FRQ)): PRINT R1$(FRQ);
13020  HTAB 20: PRINT C1$(FRQ);
13022  HTAB 32 -  LEN (R2$(FRQ)): PRINT R2$(FRQ);
13024  HTAB 35: PRINT C2$(FRQ)
13026  CALL 16742:VN = 255:VX = 0
13028  FOR N = 1 TO 5
13030 V =  PEEK (16407)
13032  IF VX < V THEN VX = V
13034  IF VN > V THEN VN = V
13036  NEXT N
13038  IF  ABS (VX - VN) > 2 THEN  GOTO 13026
13040 VL$ =  STR$ ( INT ( ABS ((VX + VN) / 2)))
13042  VTAB 21: HTAB 33: PRINT VL$;"   "
13044  RETURN
```

Ninety (90) percent of human cancers are of epithelial origin. Epithelial cells tend to line hollow organs or line the ducts of glandular tissue. Many of these organs are amenable to examination with endoscopes. For example, the bladder is accessible by a cytoscope, lungs by a bronchoscope, stomach by a gastroscope and so on. It is reasonable to expect that impedance studies can be carried out by simple modifications of these instruments placing a probe at the end of the instrument, so that measurements of capacitance can be made in patients at risk for cancer development in the different organs. The described apparatus and technique, therefore, has far reaching implications in the early detection of premalignant changes in many tissues and, as a result, have a major impact on cancer death rates.

The described techniques would be especially valuable in reducing death rates from large bowel cancer. A colonscope or sigmoidoscope modified to carry a probe of this invention can measure the

capacitance of the colonic or rectal mucosa in vivo (inside the patient) and make recommendations based on these studies. At the present time, a patient undergoes colectomy (removal of the diseased bowel) based on the presence of dysplasia (abnormal cells) or cancer. These changes often occur late and advanced cancers not amenable to cure may be found at surgery. It is believed that the altered electrical capacitance of the mucosa antecede the histologic changes by many months. or even years making secondary prevention in these patients a real possibility.

Claims

1. Apparatus for use in effecting epithelial tissue impedance measurements within a test subject, characterised by;
a first probe (10) having first and second annular electrodes (16,17) arranged in spaced relation by an intervening insulative member (19);
first and second lead wires (22.23) having an end connected respectively to the first and second annular electrodes;
a second probe (12) have third and fourth electrodes (16,17) with lead wires (22.23) connected thereto: and bridge circuit means interconnected with the lead wires of the first and second probe electrodes for measuring the epithelial electrical impedance between the probes.

2. Apparatus as in claim 1, in which the probe electrodes are constructed of silver coated with silver chloride.

3. Apparatus as in claim 1 or 2, in which the probe insulative member is constructed of polyethylene.

4. Apparatus as in claim 1,2 or 3 in which the bridge circuit means includes an amplifier having an input impedance substantially greater than that of the tissue impedance.

5. Apparatus as in any preceding claim, in which the bridge circuit means has a first stage configuration including a source of oscillatory voltage (26) with two terminals, a lead wire interconnecting the first electrode with one terminal of the oscillatory voltage source, a selectively variable resistance-capacitance impedance means (29) interconnected between the oscillatory voltage source other terminal and the second probe fourth electrode, the second and third electrodes connected as separate inputs to a first differential amplifier (31), a balancing amplifier (32) having its input interconnected with the oscillatory voltage source other terminal and its output fed into a second differential amplifier (28), lead means interconnecting the first differential amplifier output with the second differential amplifier input, the second differential amplifier output connected to a digitizing means (39), said digitizing means forming a digital signal fed into a microcomputer (33) to vary the resistance-capacitance impedance means to a value approximately the impedance of the epithelial tissue.

6. Apparatus for location within the body of a test subject to use in measuring epithelial tissue impedance, characterised by;
a generally cylindrical unitary probe (10) including in the order recited, a conical insulative nose (20), a first conductive annular electrode (16) affixed to the nose, an insulative cylinder (19) having one end secured to the first annular electrode, a second conductive annular electrode (17) secured to the insulative cylinder, and a second insulative cylinder (18) affixed to the second electrode:
a second generally cylindrical unitary probe (12) including an insulative nose (20), a first conductive annular electrode (16), an insulative cylinder (19), a second annular electrode (17) and a second insulative cylinder (18), said second probe having an outer diameter enabling receipt of said second probe within a blood vessel (13) of the subject; and
individual lead wires (22,23) connected to the first and second probe electrodes.

7. Apparatus as in claim 6, in which the probe and working electrodes are constructed of silver coated with silver chloride.

8. Apparatus for use in effecting epithelial tissue impedance measurements within a test subject, characterised by;
a first probe (10) having first and second annular electrodes (16,17) arranged in spaced relation by an intervening insulative member (19);
first and second lead wires (22,23) having an end connected respectively to the first and second annular electrodes;
a second probe (12) having third and fourth electrodes (16,17)with lead wires (22.23) connected thereto:
bridge circuit means interconnected with the lead wires of the first and second probe electrodes having a first stage configuration including a source of oscillatory voltage (26) with two terminals, a lead wire interconnecting the first electrode with one terminal of the oscillatory voltage source, a selectively variable

resistance-capacitance impedance means (29) interconnected between the oscillatory voltage source other terminal and the second probe fourth electrode. the second and third electrodes connected as separate inputs to a first differential amplifier (31) having an input impedance greater than that of the tissue impedance, a balancing amplifier (32) having its input interconnected with the oscillatory voltage source other terminal and its ouput fed into a second differential amplifier (28), lead means interconnecting the first differential amplifier output with the second differential amplifier input. the second differential amplifier output connected to a digitizing means (39), said digitizing means forming a digital signal fed into a microcomputer (33) to vary the resistance-capacitance impedance means to a value corresponding to the impedance of the epithelial tissue: and

means responsive to microcomputer control for adjusting the resistance-capacitance in impedance means to remove error impedances associated with cabling, internal equipment and circuit sources.

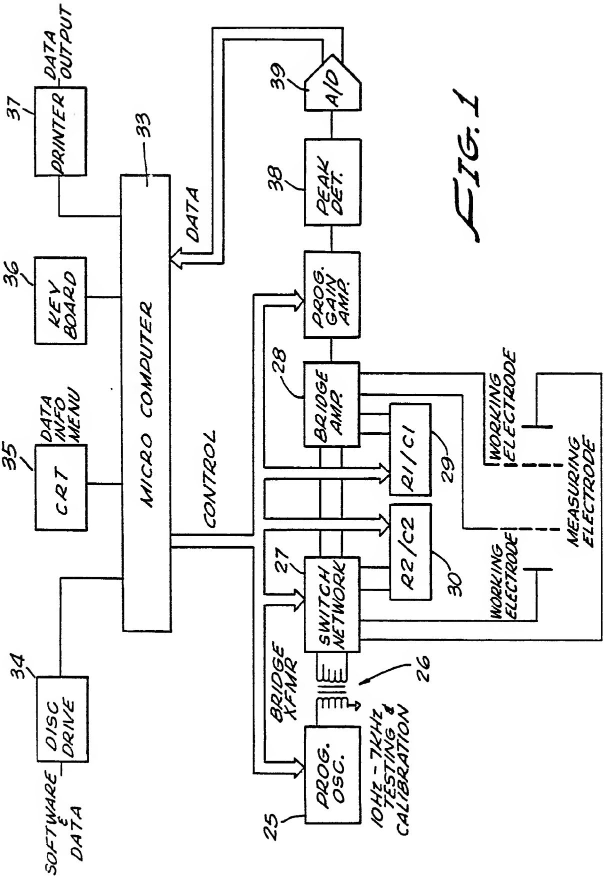

PRINTER
DATA OUTPUT
37
KEY BOARD
36
CRT
35
DATA INFO MENU
DISC DRIVE
34
SOFTWARE & DATA
MICRO COMPUTER
33
DATA
CONTROL
A/D
39
PEAK DET.
38
PROG. GAIN AMP.
BRIDGE AMP.
28
R1/C1
29
R2/C2
30
SWITCH NETWORK
27
PROG. OSC.
25
BRIDGE XFMR
26
10Hz - 7KHz TESTING & CALIBRATION
WORKING ELECTRODE
MEASURING ELECTRODE
WORKING ELECTRODE

FIG. 1

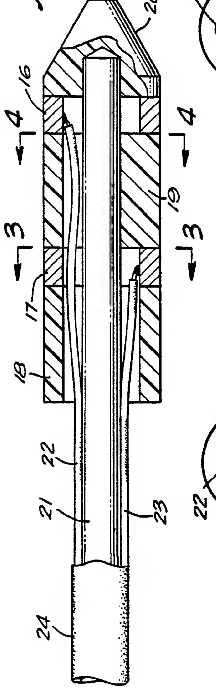


FIG. 2

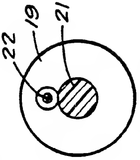


FIG. 4

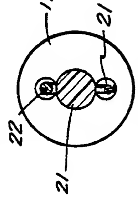


FIG. 3

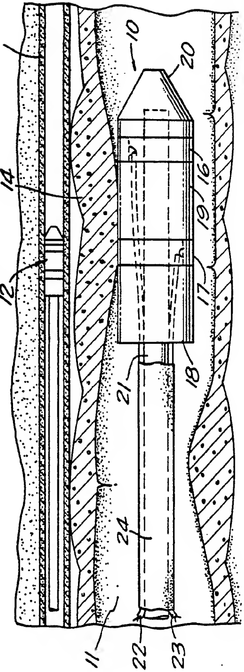
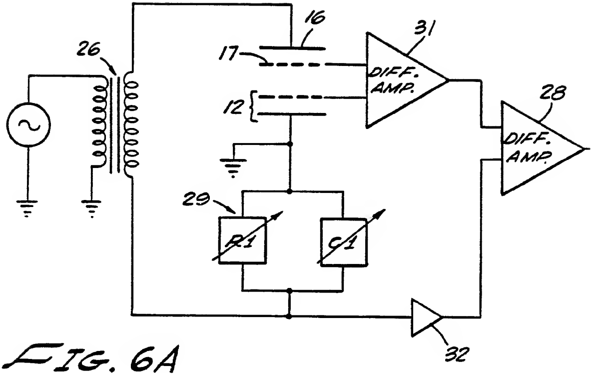
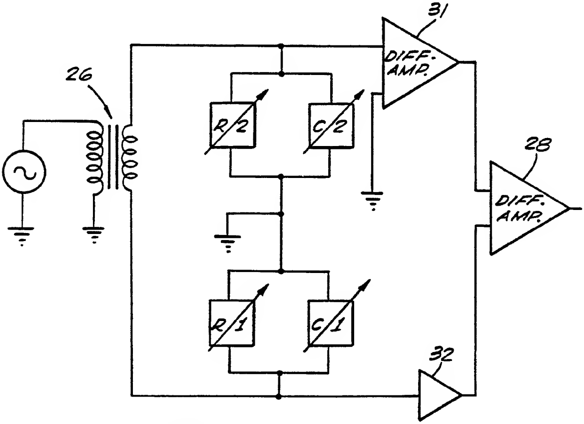


FIG. 5



16
31
26
17
DIFF. AMP.
28
12
DIFF. AMP.
29
R1
C1
32

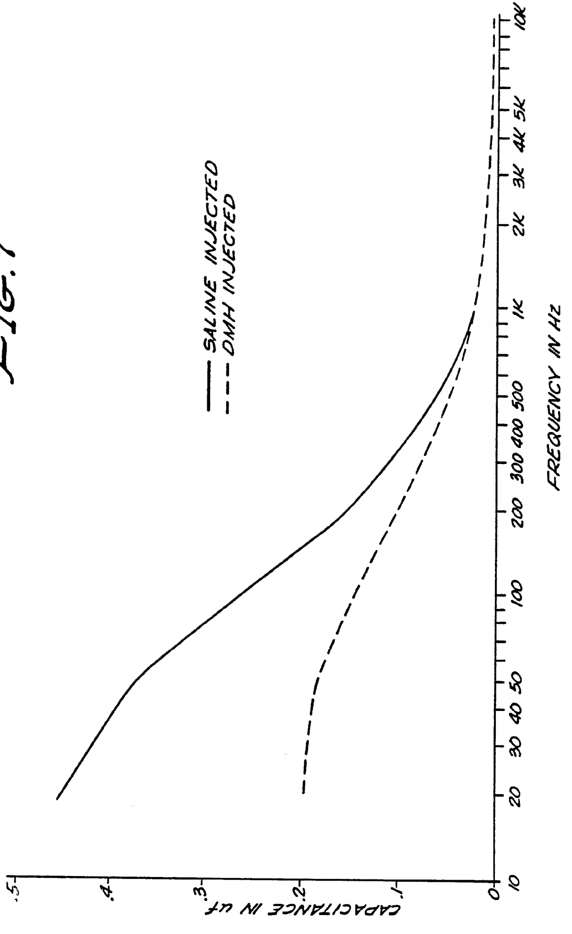
FIG. 6A



31
26
DIFF. AMP.
R2
C2
28
DIFF. AMP.
R1
C1
32

FIG. 6B

FIG. 7


SALINE INJECTED
DMH INJECTED
CAPACITANCE IN uF
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.1
.2
.3
.4
.5
FREQUENCY IN Hz
10
20
30
40
50
100
200
300
400
500
1K
2K
3K
4K
5K
10K

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EUROPEAN SEARCH REPORT

Application number

EP 87 30 0605

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int Cl 4)
Y	WO-A-8 603 391 (J.M. EVANS) * Abstract; page 8, lines 2-6; page 9, line 12 - page 11, line 4; page 18, line 16 - page 19, line 4; figures 1,3,4,15,16 *	1	A 61 B 5/05
A		5,6,8	

D,Y	MEDICAL AND BIOLOGICAL ENGINEERING, vol. 10, 1972, pages 647-654, Peter Peregrinus Ltd., Stevenage, GB; C.D. FERRIS et al.: "An operational amplifier 4-electrode impedance bridge for electrolyte measurements" * Abstract; figures 3,4 *	1	
			TECHNICAL FIELDS SEARCHED (Int. Cl 4)
D,A	Idem	4,5,8	A 61 B A 61 N

A	WO-A-8 200 581 (CORDIS CORP.) * Page 5, line 12 - page 6, line 30; page 7, lines 18-36; figures 1-3 *	1,4-6, 8	
	--- -/-		

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	18-09-1987	HUNT,B.W.

CATEGORY OF CITED DOCUMENTS

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EUROPEAN SEARCH REPORT

Application number

EP 87 30 0605

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int Cl 4)
A	AMERICAN JOURNAL OF ACUPUNCTURE, vol. 7, no. 2, April-June 1979, pages 137-144, Felton, US; J. FRADEN: "Active acupuncture point impedance and potential measurements" * Abstract; page 143, paragraph: "Electrodes"; figures 3,5 *	1,2,5, 7,8	
	-----		TECHNICAL FIELDS SEARCHED (Int. Cl 4)

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THE HAGUE	18-09-1987	HUNT,B.W.

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